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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/049,358	05/17/2002	Maria Davis	PB-9944	9975
22840 7590 01/12/2007 GE HEALTHCARE BIO-SCIENCES CORP. PATENT DEPARTMENT 800 CENTENNIAL AVENUE PISCATAWAY, NJ 08855			EXAMINER HUTSON, RICHARD G	
			ART UNIT	PAPER NUMBER
			1652	
SHORTENED STATUTORY PERIOD OF RESPONSE		MAIL DATE	DELIVERY MODE	
3 MONTHS		01/12/2007	PAPER	

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary

Application No.

10/049,358

Applicant(s)

DAVIS ET AL.

Examiner

Richard G. Hutson

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION:

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☐ Responsive to communication(s) filed on ____.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-28 is/are pending in the application.
4a) Of the above claim(s) 1-14 and 17-25 is/are withdrawn from consideration.
- 5) ☐ Claim(s) ____ is/are allowed.
- 6) ☒ Claim(s) 16 and 26-28 is/are rejected.
- 7) ☒ Claim(s) 15 is/are objected to.
- 8) ☐ Claim(s) ____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☒ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on ____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. ____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☒ Information Disclosure Statement(s) (PTO/SB/08)
Paper No(s)/Mail Date 2/02.
- 4) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date. ____.
- 5) ☐ Notice of Informal Patent Application
- 6) ☐ Other: ____.

DETAILED ACTION

Applicants preliminary amendment of claims, in the paper of 7/25/2006, is acknowledged. Claims 1-28 are still at issue and are present for examination.

Election/Restrictions

Applicant's election with traverse of Group IV, Claims 15, 16 and 26-28, drawn to a thermostable DNA polymerase corresponding to Figure 3, in the paper of 7/25/2006 is acknowledged. The traversal is on the ground(s) that Group I, claims 1, 2 and 12-14 is related to the same general inventive concept as that of the elected group (Group IV). Applicants submit that E681R was neither disclosed nor suggested in U.S. Patent No. 6,265,193 (herein below the "reference"). The reference specifically listed the suitable substitution mutations, in decreasing order of preference and E681R was not one of those listed. Applicants submit that as such, E681R defines a special technical feature over the prior art and thus Group I should be examined together with Group IV as they belong to the same group of the invention.

Applicants complete argument is acknowledged and has been carefully considered, however, is not found persuasive on the following basis. As previously stated, U.S. Patent No. 6,265,193 B1 teaches a DNA polymerase comprising a substitution corresponding to the substitution E681R. While the reference may not specifically list a suitable substitution including E681R, it remains that the reference teaches a DNA polymerase comprising a substitution corresponding to the substitution E681R. Further applicants are reminded that Group I is drawn to a thermostable DNA

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polymerase of Figure 2 (SEQ ID NO: 2), while the elected group IV is drawn to Figure 3 (SEQ ID NO: 3), and these different groups are drawn to structurally different molecules which for reasons in addition to those discussed above do not share a special technical feature.

Claims 1-14 and 17-25 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention.

Information Disclosure Statement

The listing of references in the specification is not a proper information disclosure statement. 37 CFR 1.98(b) requires a list of all patents, publications, or other information submitted for consideration by the Office, and MPEP § 609 A(1) states, "the list may not be incorporated into the specification but must be submitted in a separate paper."

Applicants filing of information disclosure statement, filed on 2/8/2002, is acknowledged. Those references considered have been initialed.

Specification

The disclosure is objected to because of the following informalities:

This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 for the reason(s) set forth: The following portions of the

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specification list sequences which appear to meet the definition for a amino acid sequence, but do not have an associated SEQ ID No: Page 4, lines 18 and 19.

Appropriate correction is required.

Claim Objections

Claims 15 and 16 are objected to because of the following informalities:

Claim 15 and 16 recite "SEQ ID No: 3". It is suggested that SEQ ID No: be amended to "SEQ ID NO:"

Appropriate correction is required.

Claim Rejections - 35 USC § 101

35 U.S.C. § 101 reads as follows:

"Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title".

Claim 16 is rejected under 35 U.S.C. § 101 because the claimed invention is directed toward non-statutory subject matter. In the absence of the hand of man, naturally occurring polypeptides (i.e. DNA polymerases) are considered non-statutory subject matter. *Diamond v. Chakrabarty*, 206 USPQ 193 (1980). This rejection may be overcome by amending the claims to contain wording such as "An isolated and purified DNA polymerase ...".

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the

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art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 16 and 26-28 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 16 and 26-28 are directed to all possible DNA polymerases comprising an amino acid substitution corresponding to the substitution E681R in the amino acid sequence listing of Figure 3 (SEQ ID No: 3). The specification, however, only provides a single representative species consisting of the DNA polymerase having the amino acid sequence of SEQ ID NO: 3, encompassed by these claims. There is no disclosure of any particular structure to function/activity relationship in the single disclosed species. The specification also fails to describe additional representative species of these polymerase mutants by any identifying structural characteristics or properties, for which no predictability of structure is apparent. Given this lack of additional representative species as encompassed by the claims, Applicants have failed to sufficiently describe the claimed invention, in such full, clear, concise, and exact terms that a skilled artisan would recognize Applicants were in possession of the claimed invention.

Applicant is referred to the revised guidelines concerning compliance with the written description requirement of U.S.C. 112, first paragraph, published in the Official Gazette and also available at www.uspto.gov.

Claims 16 and 26-28 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a DNA polymerase consisting of the amino acid sequence of SEQ ID NO: 3, does not reasonably provide enablement for any DNA polymerase comprising an amino acid substitution corresponding to the substitution E681R in the amino acid sequence listing of Figure 3 (SEQ ID No: 3). The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required, are summarized in *In re Wands* (858 F.2d 731, 8 USPQ 2d 1400 (Fed. Cir. 1988)) as follows: (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claim(s).

Claims 16 and 26-28 are so broad as to encompass any DNA polymerase comprising an amino acid substitution corresponding to the substitution E681R in the amino acid sequence listing of Figure 3 (SEQ ID No: 3). The scope of the claims is not commensurate with the enablement provided by the disclosure with regard to the extremely large number of DNA polymerase mutants broadly encompassed by the claims, including all DNA polymerases comprising an amino acid substitution corresponding to the substitution E681R in the amino acid sequence listing of Figure 3

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(SEQ ID No: 3) and variants thereof. The claims rejected under this section of U.S.C. 112, first paragraph, place minor if any structural limits, on the claimed polymerase mutants. Since the amino acid sequence of a protein determines its structural and functional properties, predictability of which changes can be tolerated in a protein's amino acid sequence and obtain the desired activity requires a knowledge of and guidance with regard to which amino acids in the protein's sequence, if any, are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification), and detailed knowledge of the ways in which the proteins' structure relates to its function. However, in this case the disclosure is limited to that DNA polymerase consisting of the amino acid sequence of SEQ ID NO: 3.

While recombinant and mutagenesis techniques are known, it is not routine in the art to screen for multiple substitutions or multiple modifications, as encompassed by the instant claims, and the positions within a protein's sequence where amino acid modifications can be made with a reasonable expectation of success in obtaining the desired activity/utility are limited in any protein and the result of such modifications is unpredictable. In addition, one skilled in the art would expect any tolerance to modification for a given protein to diminish with each further and additional modification, e.g. multiple substitutions.

The specification does not support the broad scope of the claims which encompass all modifications and fragments of any DNA polymerase comprising an amino acid substitution corresponding to the substitution E681R in the amino acid sequence listing of Figure 3 (SEQ ID No: 3) because the specification does not

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establish: (A) regions of the protein structure which may be modified without effecting the desired activity; (B) the general tolerance of DNA polymerase to modification and extent of such tolerance; (C) a rational and predictable scheme for modifying any amino acid residue of a DNA polymerase with an expectation of obtaining the desired biological function; and (D) the specification provides insufficient guidance as to which of the essentially infinite possible choices is likely to be successful. Because of this lack of guidance, the extended experimentation that would be required to determine which substitutions would be acceptable to retain the desired (i.e. polymerase) activity claimed and the fact that the relationship between the sequence of a peptide and its tertiary structure (i.e. its activity) are not well understood and are not predictable (e.g., see Ngo et al. in *The Protein Folding Problem and Tertiary Structure Prediction*, 1994, Merz et al. (ed.), Birkhauser, Boston, MA, pp. 433 and 492-495, Ref: U, Form-892), it would require undue experimentation for one skilled in the art to arrive at the majority of those polymerase mutants of the claimed genus having the claimed polymerase activity.

Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims broadly including any number of amino acid modifications of any DNA polymerase. The scope of the claims must bear a reasonable correlation with the scope of enablement (*In re Fisher*, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of those polymerase mutants having the desired biological characteristics is unpredictable and the experimentation left to those skilled in

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the art is unnecessarily, and improperly, extensive and undue. See *In re Wands* 858 F.2d 731, 8 USPQ2d 1400 (Fed. Cir, 1988).

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 16 and 26-28 are rejected under 35 U.S.C. 102(e) as being anticipated by Brandis et al. (U.S. Patent No. 6,265,193 B1).

Brandis et al. teach a DNA polymerase comprising an amino acid substitution corresponding to the substitution E681R in the amino acid sequence listing of Figure 3. Thus Brandis et al. anticipate claims 16 and 26-28.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Richard G. Hutson whose telephone number is 571-272-0930. The examiner can normally be reached on M-F, 7:00-4:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapu Achutamurthy can be reached on 571-272-0928. The fax

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phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.



Richard G Hutson, Ph.D.
Primary Examiner
Art Unit 1652

Rgh
1/8/2007